Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Recovery of functional fitness, lung function and immune function in health care workers with non-severe and severe COVID-19 at 13 months after discharge from the hospital: a prospective cohort study

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Highlights

1. COVID-19 can cause a series of clinical symptoms.
2. Lung is the organ most affected by infection of SARS-COV-2.
3. Interventions should be implemented to help recovery in HCWs with COVID-19.

Title: Recovery of functional fitness, lung function and immune function in health care workers with non-severe and severe COVID-19 at 13 months after discharge from the hospital: a prospective cohort study

A running title: Health in HCWs after discharge

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Abstract

Objective

This study aimed to evaluate the recovery of functional fitness, lung function and immune function in HCWs with non-severe and severe COVID-19 at 13 months after discharge from the hospital.

Methods

The participants of "Rehabilitation Care Project for Medical Staff Infected with COVID-19" underwent functional fitness test (muscle strength, flexibility and agility/dynamic balance), lung function test and immune function test (including cytokines and lymphocyte subsets) at 13 months

after discharge.

Results

The project included 779 HCWs (316 non-severe COVID-19 and 463 severe COVID-19). This study found 29.1% (130/446) of the HCWs as not yet recovered their functional fitness. The most affected lung function indicator was lung perfusion capacity (34% with DLCO-SB <80%). The increase of IL-6 (64/534, 12.0%) and NK cells (44/534, 8.2%), decrease of $CD3^+$ T cells (58/534, 10.9%) and $CD4^+$ T cells (26/534, 4.9%) still existed at 13 months after discharge. No significant difference was found in the HCWs with non-severe and severe COVID-19 regarding recovery of functional fitness, lung function and immune function at 13 months after discharge.

Conclusions

The majority of Chinese HCWs with COVID-19 had recovered their functional fitness, lung function, and immune function, and the recovery status in HCWs with severe COVID-19 is no worse than that in HCWs with non-severe COVID-19 at 13 months after discharge from the hospital.

Key words: novel coronavirus; COVID-19; functional fitness; cytokine; lymphocyte subsets

Introduction

COVID-19 refers to an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can cause a series of clinical symptoms, such as fever, fatigue, dry cough, dyspnea, shortness of breath, shock, and multi-organ dysfunction. As of 17 June 2022, the World Health Organization reports 535,863,950 confirmed cases of COVID-19 and 6,314,972 deaths (WHO, 2022). Between December 2019 and February 2020, 3019 health care workers (HCWs) (1716 confirmed cases) in China were found to be affected with SARS-CoV-2 (Epidemiology Working Group for NCIP Epidemic Response et al., 2020). Wuhan (17.7%) and Hubei Province (10.4%) where the patients were first diagnosed had the highest proportions of patients with severe COVID-19 in the whole country (Epidemiology Working Group for NCIP Epidemic Response et al., 2020).

At present, few studies focused on the health consequences including symptoms (Havervall et al., 2021), SARS-CoV-2 seroprevalence (Moncunill et al., 2021) and antibodies (Egbert et al., 2021) in HCWs with COVID-19 after they were discharged from the hospital. A study in China followed HCWs with COVID-19 for 3 months after discharge, it suggested that 69 (91%) of the HCWs with COVID-19 had returned to their original work, 82% of the HCWs' lung HRCTs returned to normal, and 42% of the HCWs had mild pulmonary function abnormalities (Liang et al., 2020). Our previous study reported dynamic changes of functional fitness and immunological indicators within 1 year after discharge in HCWs with severe COVID-19 (Xiong et al., 2021). There were also other studies revealing recovery of functional fitness (Paz et al.,

2021), lung function (Huang et al., 2021) and immune function (Qin et al., 2020; Wan et al., 2020) in patients with COVID-19. However, most of these studies were not carried out in HCWs with COVID-19, and few of them had compared the recovery status in patients between non-severe and severe COVID-19 after discharge. In the fight against COVID-19, HCWs with COVID-19 had made huge sacrifices. It is of great public health significance to pay attention to their health status after discharge from the hospital, and to implement individualized interventions in helping the recovery of the target population. So far, the health consequences of HCWs with COVID-19 at 13 months after discharge from the hospital remain unclear.

Therefore, this study aimed to evaluate the recovery of functional fitness, lung function and immune function in HCWs with COVID-19 at 13 months after discharge from the hospital, and to compare the recovery status between participants in non-severe and severe group.

Methods

Study design and participants

The participants were from the "Rehabilitation Care Project for Medical Staff Infected with COVID-19" in China, it was launched by the Chinese Academy of Engineering and Tencent Charity Foundation (Xiong et al., 2021). The participants were HCWs with COVID-19 in Hubei

Province (including the provincial capital city Wuhan and its surrounding cities). The HCWs with COVID-19 agreed to participate in the project through the information platform of "Rehabilitation Care Project for Medical Staff Infected with COVID-19", and were followed up on the health consequences after discharge from the hospital. The health consequences which the project mainly focused on included psychological evaluation, survey of persistent symptoms, lung function evaluation, and physical examinations. From June 2020 to March 2021, the project included a total of 779 HCWs (316 non-severe and 463 severe COVID-19), and all HCWs were contacted through the platform and/or by telephone to participate in follow-up visits (5, 8, 11, and 13 months after discharge) in Union Hospital (Tongji Medical College, Huazhong University of Science and Technology). Currently, the longest follow-up period for the HCWs is 13 months after discharge.

Regarding follow-up visits at 13 months after discharge, all HCWs participating in this project were asked to take physical examinations (any time between 11 March 2021 and 19 March 2021), and complete the functional fitness, lung function, and immune function tests at Union Hospital (Tongji Medical College, Huazhong University of Science and Technology). For HCWs with abnormal results of physical examinations, experts will be arranged to develop personalized rehabilitation plans for them to speed recovery.

In this study, HCWs of "Rehabilitation Care Project for Medical Staff Infected with COVID-19" who completed any of the follow-up visits

(including functional fitness test, lung function test and immune function test) between 11 March 2021 and 19 March 2021 were included in the analyses.

The disease severity and the standards of discharge were evaluated according to the recommendations by the National Health Commission (China National Health Commission, 2020). The severity of the disease was divided into 4 types including mild (with mild clinical symptoms but without pneumonia manifestations in imaging examination), moderate (with fever, respiratory symptoms, etc., and with pneumonia manifestations in imaging examination), severe (meeting at least one of the following criteria: shortness of breath, RR ≥30 beats/min; the oxygen saturation ≤93%; $PaO_2/FiO_2 \leq 300$ mmHg in the resting state), and critical (meeting at least one of the following criteria: respiratory failure requiring mechanical ventilation; shock; combined with other organ failure requiring ICU monitoring and treatment). In this study, the HCWs with severe or critical COVID-19 were assigned to the severe group, and the HCWs with mild or moderate COVID-19 were assigned to the non-severe group. The standards of discharge included 1) no fever for three consecutive days, 2) improved respiratory symptoms, 3) obvious resolution and recovery of acute lesion in lung CT scanning, and 4) two negative results of SARS-CoV-2 tests 24 hours apart.

According to the principles of the Declaration of Helsinki, this research was approved by the Ethics Committee of Union Hospital, Tongji

Medical College, Huazhong University of Science and Technology. All HCWs signed informed consents at enrollment.

Data collection

Information on demographic and clinical characteristics of the participants was obtained at enrollment through the information platform of "Rehabilitation Care Project for Medical Staff Infected with COVID-19".

The functional fitness test was performed by doctors in the Department of Rehabilitation of Union Hospital (Tongji Medical College, Huazhong University of Science and Technology). Given that the Senior Fitness Test (SFT) could comprehensively reflect the physical recovery status of the participants in the aspects of muscle strength, flexibility and agility/dynamic balance. Previous literature showed that SFT could also be applied in other age groups beyond the elderly (Boshnjaku et al., 2021), therefore, this study used SFT to assess the functional fitness status. In this study, the SFT included evaluation of muscle strength (grip strength test, 30-second elbow flexion test, 30-second chair stand and 2-minute step test), flexibility (back scratch test and chair sit-and-reach test) and agility/dynamic balance (functional reach test, YBT and the Y balance test) (Rikli and Jones 1999). According to literature and policy documents, there are normal ranges for evaluation of muscle strength and agility/dynamic balance (Nogueira et al., 2021; State Sport Genearl Administration, 2003). Therefore, if a HCW's score in any test of muscle

strength and agility/dynamic balance is out of the normal ranges, it was recorded that they had not recovered their functional fitness by the doctors.

The lung function test was performed by doctors at the NHC Key Laboratory of Pulmonary Diseases of Union Hospital (Tongji Medical College, Huazhong University of Science and Technology). The tests were performed with the Masterscreen pneumotachograph system (CareFusion, Hoechberg, Germany), and the diagnoses were based on the recommendations by American Thoracic Society (Graham et al., 2019).

The immunological indicators of the HCWs were measured at the Department of Clinical Laboratory of Union Hospital (Tongji Medical College, Huazhong University of Science and Technology). The levels of cytokine profile including IFN-γ, IL-10, IL-2, IL-4, IL-6 and TNF-α were quantified by BD cytometric bead array analysis using the BD™ Cytometric Bead Array (CBA) Human Th1/Th2 cytokine kit. The relative numbers of lymphocyte subsets including B cells, $CD3^+$ T cells, $CD4^+$ T cells, $CD4^+/CD8^+$ cell ratio, $CD8^+$ T cells and NK cells were detected with flow cytometry (BD FACSCanto™, BD Biosciences), and data of lymphocyte subsets were analyzed with FCAP software (version 3.0).

Statistical analysis

Median and IQR (interquartile range) and number (%) were used to describe continuous and categorical covariates, respectively. The Mann-Whitney U test, Wilcoxon signed-rank test, t test, χ^2, and Fisher's exact test were applied where appropriate. Multivariate linear regression models were utilized in analyzing the associations of disease severity with functional fitness. Multivariable adjusted logistic regression models were applied in investigating the relationships of disease severity and lung function. The covariates of age, sex, education, roles in work, body mass index (BMI), smoking habit and comorbidities were adjusted in the models. The analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and a two-sided *P* value lower than 0.05 was considered to be statistically significant.

Results

Characteristics of the HCWs

From June 2020 to March 2021, the cohort recruited a total of 779 HCWs in Hubei Province. All the follow-up visits were completed between 11 March 2021 and 19 March 2021. The median number of days of discharge from the hospital was 387.4 (376.3, 396.3) (approximately 13 months). Among the 779 HCWs, 222 HCWs missed follow-up visits at 13 months after discharge. Among the remaining 557 HCWs, 111 HCWs declined functional fitness test, 254 HCWs declined lung function test, and 23 HCWs declined immune function test. The final sample sizes of participants who underwent functional fitness, lung function and immune function tests (including cytokines and lymphocyte subsets) were 446,

303 and 534, respectively (Figure 1).

The demographic and clinical characteristics of 779 HCWs according to disease severity were presented in Table 1. The HCWs' median age was 35.0 (30.0-43.0) years, median BMI was 22.8 (20.8-25.2) kg/m^2, 77% of the HCWs were female (601/779), and 59% (445/755) of the HCWs were nurses. The HCWs with severe COVID-19 were older, had higher BMI, lower education status, less likely to be nurses, more likely to have respiratory support, history of ICU admission, comorbidities, and symptoms at admission than HCWs with non-severe COVID-19.

Functional fitness in HCWs with non-severe and severe COVID-19

In this study, 446 HCWs (162 non-severe and 284 severe COVID-19) took part in the test of functional fitness, it found 29.1% (130/446) of the HCWs as not yet recovered their functional fitness. There was no significant variance in the proportion of unrecovered HCWs between the non-severe (30.2%, 49/162) and severe group (28.5%, 81/284). The results of functional fitness test in HCWs according to disease severity were presented in Table 2. In the three aspects of functional fitness recovery (muscle strength, flexibility and agility/dynamic balance), no significant difference was found in the non-severe and severe group (all *P* values >0.05). The characteristics of the HCWs included and excluded from the analyses of functional fitness were similar (Table S1).

Lung function in HCWs with non-severe and severe COVID-19

A total of 303 HCWs (114 non-severe and 189 severe COVID-19) underwent lung function test at 13 months after discharge. The lung function indicators of the HCWs according to disease severity were demonstrated in Table 3. This study found that the most affected indicator of lung function was lung perfusion capacity (34% with DLCO-SB <80%) in the HCWs. Obstruction (FEV_1/FVC<70%) was found in 8%, and restriction (TLC-SB <80%) in 6% of the HCWs. No significant variance in all indicators of lung function was found in HCWs of different disease severity (all *P* values >0.05). The characteristics of the HCWs included and excluded from the analyses of lung function were similar (Table S1).

Immune function in HCWs with non-severe and severe COVID-19

In this study, 534 HCWs (198 non-severe and 336 severe COVID-19) participated in the test of immune function. No significant difference was found in the median values of cytokines (Table 4) and lymphocyte subsets (Table 5) between the non-severe and the severe group. This study also analyzed the distribution of various cytokines and lymphocyte subsets. The results suggested that more than 95% of the study population had normal levels of IFN-γ, IL-10, IL-2, IL-4 and TNF-α, and 12.0% (64/534) of the HCWs had elevated levels of IL-6 at 13 months after discharge from the hospital (Table 4). More than 90% of the HCWs had normal relative numbers of lymphocyte subsets (B cells, $CD3^+$ T cells,

$CD4^+$ T cells, $CD4^+/CD8^+$ cell ratio, $CD8^+$ T cells and NK cells) (Table 5). At 13 months after discharge from the hospital, the decrease of $CD3^+$ T cells (58/534, 10.9%) and $CD4^+$ T cells (26/534, 4.9%), and elevation of NK cells (44/534, 8.2%) still existed.

This study compared the levels and distributions of cytokines and lymphocyte subsets in HCWs with non-severe and severe COVID-19, and found no statistically significant differences between the two groups (all *P* values >0.05). This study also compared the levels of cytokines in 152 HCWs with severe COVID-19 at 11 months and 13 months after discharge. Results showed that levels of all cytokines except IL-2 were lower at 13 months after discharge than at 11 months. Levels of IL-2 were slightly elevated within normal ranges at 13 months after discharge compared with 11 months (Table S2). The characteristics of the HCWs included and excluded from the analyses of immune function were similar (Table S1).

Discussion

As far as we know, this is the first study that focuses on the health consequences of patients with COVID-19 with the longest follow-up time (13 months after discharge), and the study population is HCWs. This study found that at 13 months after discharge from the hospital, there was no statistically significant difference between the HCWs in non-severe and severe group regarding recovery of functional fitness, lung function and

immune function. The results of this study found that at 13 months after discharge, a small proportion of HCWs had not recovered their functional fitness (about 30%), had poor lung perfusion (34%), increased IL-6 and NK cells, decreased relative numbers of $CD3^+$ T cells and $CD4^+$ T cells. Interventions should be implemented timely to help speed recovery in these target population in the future.

In the present study, approximately 30% of the HCWs had not recovered their functional fitness at 13 months after discharge from the hospital. The results were consistent with the findings of an Italian study which demonstrated that 32% of the patients were still showing an impaired functional fitness up to 3~6 months after infection of SARS-CoV-2 (Baricich et al., 2021). The decline in functional fitness was also found in patients with SARS 1~2 years after discharge from the hospital (Rooney et al., 2020). Studies speculated that the causes of the decline in functional fitness might be related to the prolonged time of immobility (Herridge et al., 2016), the impairment in lung function (Mo et al., 2020), the presence of neurological symptoms such as skeletal muscle injury (Cagnazzo et al., 2021), and the inflammatory changes due to cardiac involvement (Cruz Rodriguez et al., 2020). To date, it is not clear how COVID-19 affects the functional fitness of the patients, and for how long the impaired functional fitness will last. Therefore, researches regarding mechanisms and with a longer follow-up time should be carried out in the future. Additionally, rehabilitation guidance should be provided to help their recovery.

Our study found that up to 34% of the HCWs with COVID-19 had diffusion impairment at 13 months after discharge. Similar to the previous findings, lung is the organ most affected by infection of SARS-COV-2, and former studies also found abnormal lung function in patients with COVID-19 after discharge or symptom onset (Huang et al., 2021; Milanese et al., 2021; Shah et al., 2021). The study in Jin Yin-tan Hospital in China reported that 22~56% of patients with various severity scales of COVID-19 had pulmonary diffusion abnormality (DLCO <80%, % of predicted) at six months after symptom onset (Huang et al., 2021). A study in Italy also found that 40% of the patients with COVID-19 had DLCO impairment at 6 months after hospital discharge (Milanese et al., 2021). Another prospective cohort in Canada suggested that more than 50% of the patients with COVID-19 had lung function impairment at 12 weeks after symptom onset (Shah et al., 2021). In published studies, patients with SARS (Xie et al., 2005) and H1N1 (Bai et al., 2011) were also found to have varying degrees of decline in lung diffusing capacity after discharge, and the impairment would persist for months or years after discharge. Therefore, it is of significant importance to monitor lung function in patients with COVID-19 after discharge from the hospital for a longer period of time. Additionally, effective intervention measures such as cardiopulmonary exercise (Gao et al., 2021) should be practiced to help patients regain their regular lung function. Some studies speculate that the mechanisms of the decreased diffusing capacity caused by SARS-COV-2 may be related to angiotensin-converting enzyme 2, the lung and multi-organ damage, and functional failure caused by cytokine storm (Iwasaki et al., 2021; Mustafa et al., 2020), and related mechanism research should also be further carried out.

Patients infected with the SARS-COV-2 (Qin et al., 2020; Wan et al., 2020), SARS-COV (Huang et al., 2005), H7N9 (Zhou et al., 2013) and H5N1 (Henter et al., 2006) were found to have increased levels of cytokines (especially IL-6) which indicated an uncontrolled systemic inflammatory reaction process, and might lead to severe immune pathological damage. Similar to the present study, a study in China demonstrated that two weeks post recovery, patients with COVID-19 had elevated levels of IL-6 (20.59%), IL-4 (19.12%), TNF-α (10.29%), IL-17 (2.94%) and IL-10 (1.47%) while levels of cytokine in healthy controls were all in normal ranges (Hasichaolu et al., 2020). Another study in China compared the levels of cytokines in hospitalized and discharged patients with non-critical COVID-19, it reported that the levels of IL-6, TNF-α, IFN-γ, IL-2, IL-4, and IL-10 were all upregulated in the hospitalized patients (Lin et al., 2020). In our previous research, we explored the cytokine levels in HCWs with severe COVID-19 before discharge, at 5 months, 8 months, and 11 months after discharge. The results suggested that the majority of the HCWs' cytokine levels gradually returned to normal (showed a trend of decline) (Xiong et al., 2021). The cytokine levels still showed a trend of decline from 11 months to 13 months in HCWs with severe COVID-19. At 11 months after discharge, about one-third of HCWs with severe COVID-19 had elevated cytokine levels (Xiong et al., 2021). In this study, it was found that at 13 months after discharge, only 12% of the HCWs (including non-severe and severe COVID-19) had increased cytokine levels (only IL-6 increased), indicating that the cytokines recovered well in the majority of the participants regardless of disease severity. This study found for the first time that the recovery of

cytokine levels in HCWs with non-severe and severe COVID-19 at 13 months after discharge from the hospital was similar, indicating that the immune function of HCWs with severe COVID-19 could also be recovered as well as those with non-severe COVID-19. However, the specific mechanism is still unclear, and mechanism researches should be carried out to further explore the recovery process.

This study found that at 13 months after discharge, the relative numbers of $CD3^+$ T cells, $CD4^+$ T cells, $CD8^+$ T cells decreased and NK cells increased in HCWs regardless of disease severity. This is similar to our previous results in follow-up visits within 1 year (Xiong et al., 2021), but the lymphocyte subsets at 13 months after discharge recovered better than that within 1 year in HCWs. In addition to our previous study, there were also other researches indicating that the immune system gradually recovered after COVID-19 infection. A study in China found decreased levels of $CD8^+$ T cells, $CD19^+$ B cells, total lymphocytes, $CD3^+$ T cells, $CD4^+$ T cells and $CD56^+$ NK cells in COVID-19 patients two weeks post recovery (Hasichaolu et al., 2020). Another study in China suggested that the levels of neutrophils, monocytes, NK cells, and $CD4^+$ T cells increased, and levels of total lymphocytes and $CD8^+$ T cells significantly decreased in discharged non-critical patients with COVID-19 than those hospitalized (Lin et al., 2020). Published studies showed that levels of lymphocyte subsets were significantly decreased in patients with severe COVID-19 (Huang et al., 2020; Wang et al., 2020). Lymphocytes play key roles in viral clearance in patients with COVID-19. The observed decrease of lymphocyte subsets may destroy many immune cells, and then inhibit the patients' cellular immunity. The decreases in

lymphocyte subsets post recovery were evidenced to be independent predictors of disease severity and rehabilitation efficacy (Akbari et al., 2020; Deng et al., 2020; Wan et al., 2020; Wang et al., 2020). Similar T cell depletion was also observed in patients with SAR-CoV and MERS patients (Fung et al., 2020). However, the mechanisms remain unclear though there were studies speculating that cytokine storm (Zhang et al., 2020), lung impairment and virus (Merad and Martin, 2020) might be involved in the T cell depletion. Future mechanism studies are warranted. Studies with a longer follow-up time are also needed to investigate the impacts of COVID-19 on immune function.

This research has several limitations. Firstly, this study evaluated the HCWs' functional fitness recovery from three aspects including muscle strength, flexibility, and agility/dynamic balance. Follow-up studies should also use other evaluation methods such as the 6-minute walking test to evaluate the HCWs' functional fitness recovery. Secondly, the HCWs did not have lung function test before infection and therefore it was impossible to make a comparison with the results after infection. The number of the HCWs with chronic respiratory disease was limited though self-reported prevalence of chronic respiratory disease might lead to underestimation. This study speculates that the majority of the HCWs' lung function at baseline is normal. The interpretation of current results remains valid. Thirdly, this study did not analyze the associations between CT findings and lung function parameters, future studies should focus on these aspects. Fourthly, due to the methods of laboratory testing, only the relative numbers of lymphocyte subsets were available in this study. Follow-up studies should also continue to focus on the differences in the

absolute numbers of lymphocyte subsets. Fifthly, this study lacked a control group and could not assess the health status in HCWs who were not infected with COVID-19. Future studies should be carried out to compare the health status of HCWs infected and uninfected with COVID-19. Lastly, this study found that there was no statistically significant difference in some aspects of health recovery in HCWs with non-severe and severe COVID-19. The response rate of follow-up visits may introduce biases to the study findings, though the characteristics of the HCWs included and excluded from the study were similar. Additionally, the low proportion of ICU admission (4%) in HCWs with severe COVID-19 and the high proportion (approximately 40%) of HCWs without supplemental oxygen may also limit generalizability of the study findings to other population. Therefore, the results achieved in the current study need to be confirmed in larger cohort studies in the future.

At 13 months after discharge from the hospital, the health consequences of the majority of the HCWs with COVID-19 had returned to normal, and the recovery of HCWs with severe COVID-19 is no worse than those with non-severe COVID-19 in terms of functional fitness, lung function, and immune function. However, it is still necessary to implement interventions timely in helping HCWs to recover fully after discharge from the hospital.

List of abbreviations

BMI: body mass index

DLCO: diffusion capacity for carbon monoxide

FEV_1: forced expiratory volume in one second

FRC: functional residual capacity

FVC: forced vital capacity

HCWs: health care workers

ICU: intensive care unit

IQR: interquartile range

RV: residual volume

SFT: Senior Fitness Test

TLC: total lung capacity

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Compliance with ethics guidelines

Lijuan Xiong, Qian Li, Xiongjing Cao, Huangguo Xiong, Ming Huang, Fengwen Yang, Daquan Meng, Mei Zhou, Yanzhao Zhang, Yunzhou Fan, Liang Tang, Yang Jin, Jiahong Xia and Yu Hu declared no competing interests. According to the principles of the Declaration of Helsinki, this research was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. All HCWs signed informed consents at enrollment.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files]. Since the cohort is still going on, we may not make the data available to others.

Contributors

Hu Y, Xia J, Xiong LJ, Li Q, Cao XJ, Xiong HG, Huang M and Yang FW designed this study. Hu Y, Xiong LJ and Li Q were responsible for the integrity of the data and the accuracy of the data analysis. All authors had full access to all of the data in the study. Hu Y, Xia J and Xiong LJ managed the project and provided guidance. Xiong LJ, Cao XJ, Xiong HG, Meng DQ, Zhou M, Zhang YZ and Fan YZ collected the data. Xiong LJ, Li Q, Xiong HG and Tang L analyzed the data. Xiong LJ and Li Q drafted the manuscript. All authors revised the manuscript and gave final approval for the version to be published.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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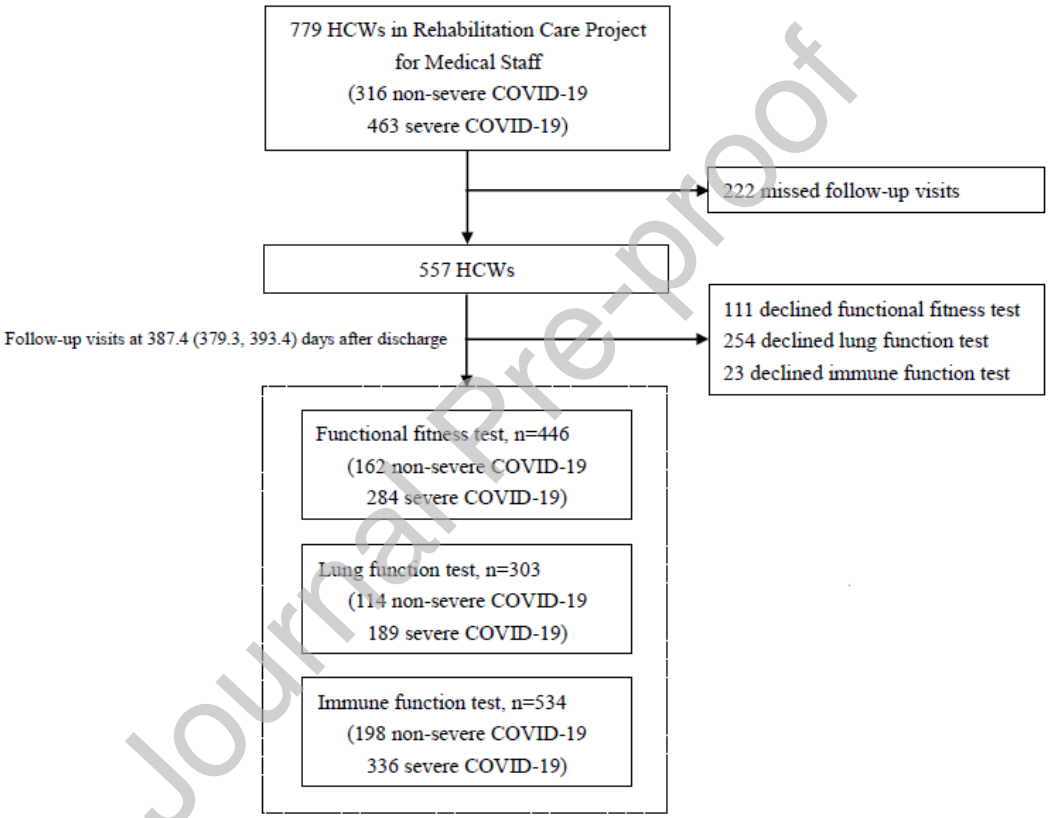

Figure 1-Flow chart of this study

HCWs: health care workers

Table 1-Characteristics of HCWs according to disease severity of COVID-19

Characteristics	All (N=779)	Non-severe (N=316)	Severe (N=463)	*P*
Demographic characteristics				
Age (years)	35.0 (30.0-43.0)	34.0 (28.0-40.0)	36.0 (31.0-45.0)	<0.001
BMI (kg/m^2)	22.8 (20.8-25.2)	22.0 (20.0-23.8)	23.4 (21.2-25.7)	<0.001
Sex (female)	601 (77%)	249 (79%)	352 (76%)	0.386
Education (College and higher)	586/732 (80%)	234/288 (81%)	352/444 (79%)	0.019
Location of the hospital work for				0.378
Hankou, Wuhan	452 (58%)	188 (59%)	264 (57%)	
Wuchang, Wuhan	196 (25%)	79 (25%)	117 (25%)	
Hanyang, Wuhan	40 (5%)	11 (4%)	29 (6%)	
Outside Wuhan in Hubei	91 (12%)	38 (12%)	53 (12%)	
Roles in work				0.003
Doctors	184/755 (24%)	72/298 (24%)	112/457 (24%)	
Nurses	445/755 (59%)	182/298 (61%)	263/457 (58%)	
Other	126/755 (17%)	44/298 (15%)	82/457 (18%)	
Smoke habit (yes)	24/756 (3%)	9/300 (3%)	15/456 (3%)	0.016
Time from discharge to follow-up (days)*	387.4 (379.3-393.4)	386.4 (382.3-396.1)	387.4 (379.1-393.3)	0.271
Clinical characteristics				
The highest respiratory support in hospital				<0.001
No supplemental oxygen	278/740 (38%)	159/295 (54%)	119/445 (27%)	

Supplemental oxygen by nasal cannula or mask	443/743 (60%)	136/295 (46)	307/445 (69%)	
Non-invasive or invasive mechanical ventilation	19/740 (2%)	0(0%)	19/445 (4%)	
ICU admission (yes)	20/753 (3%)	1/299 (0.3%)	19/454 (4%)	<0.001
Comorbidities (yes)	167/747 (22%)	28/298 (9%)	139/449 (31%)	<0.001
Symptoms at admission				
Fatigue	412 (53%)	127 (60%)	285 (62%)	<0.001
Fever	404 (52%)	119 (38%)	285 (62%)	<0.001
Muscle soreness	252 (32%)	58 (18%)	194 (42%)	<0.001
Dry cough	238 (31%)	79 (25%)	159 (34%)	0.006
Cough	232 (30%)	72 (23%)	160 (35%)	<0.001
Chest distress	212 (27%)	49 (16%)	163 (35%)	<0.001
Diarrhoea	175 (23%)	56 (18%)	119 (26%)	0.009
Shortness of breath	169 (22%)	29 (9%)	140 (30%)	<0.001
Headache	147 (19%)	33 (10%)	114 (24%)	<0.001
Dyspnoea	99 (13%)	7 (2%)	92 (20%)	<0.001
Vomiting	43 (6%)	8 (3%)	35 (8%)	0.002

Data are presented as n (%), n/N (%), or median (IQR). BMI: body mass index. HCWs: health care workers. ICU: intensive care unit. IQR: interquartile range

*The sample sizes for group of “all”, “non-severe ” and “severe” were 557, 205 and 352.

Table 2-Functional fitness in HCWs with non-severe and severe COVID-19

Categories	All (N=446)	Median (IQR)		β (95% CI)		*P*
		Non-severe (N=162)	Severe (N=189)	Non-severe (N=114)	Severe (N=189)	
Muscle strength test						
Grip strength test, N	25.5 (21.2, 30.5)	25.9 (21.4, 29.9)	25.3 (21.3, 30.7)	0	0.21 (-0.98, 1.41)	0.726
30-second elbow flexion test, n	19.0 (15.0, 20.5)	18.0 (15.0, 24.0)	19.0 (15.0, 23.0)	0	0.21 (-0.83, 1.24)	0.693
30-second chair stand, n	17.0 (15.0, 20.5)	18.0 (15.0, 21.0)	17.0 (15.0, 20.0)	0	-0.50 (-1.50, 0.50)	0.328
2-minute step test, n	93.0 (80.0, 107.0)	95.0 (83.0, 108.0)	92.0 (79.0, 107.0)	0	-1.62 (-5.60, 2.36)	0.423
Flexibility test						
Back scratch test (left)	-1.0 (-8.0, 3.0)	0.0 (-5.9, 3.4)	-2.8 (-10.1, 2.6)	0	-0.76 (-2.51, 0.99)	0.392
Back scratch test (right)	2.0 (-2.1, 5.0)	2.5 (0.0, 5.2)	1.7 (-4.3, 4.4)	0	-1.01 (-2.39, 0.36)	0.147
Chair sit-and-reach test, cm	1.5 (-2.0, 6.5)	2.3 (0.0, 7.0)	1.0 (-3.5, 6.5)	0	0.05 (-2.38, 2.48)	0.969
Agility/dynamic balance						
Functional reach test, cm	27.0 (22.2, 31.0)	27.0 (22.0, 30.0)	27.0 (23.0, 31.0)	0	0.51 (-0.97, 1.99)	0.500
YBT						
Anterior-L*	73.1 (69.0, 80.0)	73.0 (69.4, 79.0)	73.5 (68.0, 80.0)	0	0.56 (-1.13, 2.26)	0.512

Posterolateral-L	76.0 (70.2, 81.0)	75.9 (71.0, 81.0)	77.0 (70.0, 81.0)	0	0.52 (-1.40, 2.45)	0.595
Posteromedial-L	64.0 (54.9, 71.8)	64.0 (56.0, 71.0)	77.0 (70.0, 81.0)	0	1.01 (-1.67, 3.71)	0.460
Anterior-R†	75.0 (69.5, 80.0)	75.0 (70.5, 80.0)	75.0 (69.0, 80.0)	0	-0.27 (-1.85, 1.31)	0.731
Posterolateral-R	78.0 (71.5, 83.0)	78.0 (73.0, 83.0)	78.0 (71.0, 84.0)	0	0.00 (-1.87, 1.87	0.999
Posteromedial-R	62.0 (54.0, 70.0)	61.0 (54.0, 81.0)	63.0 (54.0, 71.0)	0	1.29 (-1.42, 3.99)	0.351
Leg length	79.0 (76.8, 81.5)	79.0 (76.8, 81.0)	79.0 (76.8, 81.6)	0	0.25 (-0.28, 0.77)	0.358
Composite score-L	211.8 (196.6, 227.0)	211.0 (197.9, 228.4)	212.0 (196.5, 227.9)	0	2.10 (-2.80, 7.00)	0.400
Composite score-R	214.0 (197.0, 229.6)	214.0 (197.9, 228.4)	214.0 (196.0, 230.0)	0	1.01 (-4.01, 6.03)	0.692
Ratio of composite score to leg length-L	0.9 (0.8, 0.9)	0.9 (0.8, 0.9)	0.9 (0.8, 0.9)	0	0.01 (-0.01, 0.02)	0.533
Ratio of composite score to leg length-R	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	0	0.00 (-0.02, 0.02)	0.931

HCWs: health care workers. IQR: interquartile range. *L-reach distance by left leg. †R-reach distance by right leg.
The models adjusted for age, sex, education, roles in work, body mass index (BMI), smoke habit and comorbidities.

Table 3-Lung function in HCWs with non-severe and severe COVID-19

Categories	All (N=303)	N (%)		β (95% CI)		*P*
		Non-severe (N=114)	Severe (N=189)	Non-severe (N=114)	Severe (N=189)	
FEV_1 <80%, % of predicted	24 (8%)	13 (11%)	11 (6%)	1	0.51 (0.20, 1.31)	0.160
FVC <80%, % of predicted	7 (2%)	4 (4%)	3 (2%)	1	0.57 (0.08, 4.29)	0.583
FEV_1/FVC <70%	24 (8%)	9 (8%)	15 (8%)	1	1.11 (0.43, 2.84)	0.827
RV <80%, % of predicted*	43 (14%)	17 (15%)	26 (14%)	1	0.75 (0.36, 1.57)	0.449
TLC <80%, % of predicted	18 (6%)	9 (8%)	9 (5%)	1	0.51 (0.17, 1.57)	0.243
FRC <80%, % of predicted	57 (19%)	17 (15%)	40 (21%)	1	1.52 (0.77, 3.00)	0.223
DLCO <80%, % of predicted*	102 (34%)	42 (37%)	60 (32%)	1	0.71 (0.41, 1.23)	0.223

Data are presented as n (%). *Carbon monoxide diffusion capacity was not corrected for haemoglobin.

DLCO: diffusion capacity for carbon monoxide. FEV_1: forced expiratory volume in one second. FRC: functional residual capacity. FVC: forced vital capacity. HCWs: health care workers. RV: residual volume. TLC: total lung capacity.

The models adjusted for age, sex, education, roles in work, body mass index (BMI), smoke habit and comorbidities.

Table 4-Levels of cytokines in HCWs with non-severe and severe COVID-19

Categories	All (N=534)	Non-severe (N=198)	Severe (N=336)	*P*
IFN-γ (pg/mL)	1.04 (0.96-1.16)	1.04 (0.96-1.16)	1.04 (0.96-1.16)	0.881
Elevated	1 (0.2%)	1 (0.5%)	0 (0.0%)	
Normal*	0.64-15.17	0.73-15.17	0.64-9.58	0.371
Decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	
IL-10 (pg/mL)	1.25 (1.09-1.45)	1.25 (1.10-1.45)	1.40 (1.05-1.45)	0.952
Elevated	3 (0.6%)	2 (1.0%)	1 (0.3%)	
Normal*	0.51-3.81	0.66-2.55	0.51-3.81	0.559
Decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	
IL-2 (pg/mL)	1.36 (1.23-1.52)	1.36 (1.25-1.48)	1.40 (1.23-1.52)	0.271
Elevated	3 (0.6%)	2 (1.0%)	1 (0.3%)	
Normal*	0.87-4.07	0.87-4.07	0.91-4.07	0.558
Decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	
IL-4 (pg/mL)	1.50 (1.39-1.61)	1.46 (1.35-1.61)	1.50 (1.39-1.60)	0.598
Elevated	1 (0.2%)	1 (0.5%)	0 (0.0%)	0.371
Normal*	1.02-2.60	1.02-2.48	1.04-2.60	

Decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	
IL-6 (pg/mL)	1.53 (1.20-2.55)	1.51 (1.20-2.44)	1.62 (1.14-2.74)	0.589
Elevated	64 (12.0%)	25 (12.6%)	39 (11.6%)	
Normal*	0.32-5.25	0.32-5.25	0.48-5.23	0.783
Decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	
TNF-α (pg/mL)	2.58 (1.60-5.60)	2.49 (1.60-6.45)	2.58 (1.58-5.08)	0.596
Elevated	8 (1.5%)	3 (1.5%)	5 (1.5%)	
Normal*	0.56-21.20	0.56-21.20	0.92-20.38	0.980
Decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	

Data are presented as median (IQR). *Data are shown as the normal ranges of the indicators. HCWs: health care workers. The comparison between two groups was performed with Mann–Whitney U test.

Table 5-Levels of lymphocyte subsets in HCWs with non-severe and severe COVID-19

Categories	All (N=534)	Non-severe (N=198)	Severe (N=336)	*P*
B cells (%)	9.90 (7.79-12.30)	9.90 (7.85-12.08)	9.90 (7.72-12.42)	0.963
Elevated	12 (2.2%)	5 (2.5%)	7(2.1%)	
Normal*	4.29-18.31	4.29-17.60	4.30-18.31	0.918
Decreased	15 (2.8%)	6 (3.0%)	9 (2.7%)	
$CD3^+$ T cells (%)	70.67 (64.37-75.92)	71.17 (65.15-76.40)	70.04 (63.92-75.55)	0.254
Elevated	7 (1.3%)	0 (0.0%)	7(2.1%)	
Normal*	58.21-83.83	58.34-82.80	58.21-83.83	0.068
Decreased	58 (10.9%)	18 (9.1%)	40 (11.9%)	
$CD4^+$ T cells (%)	35.58 (31.01-40.36)	36.40 (31.49-40.10)	35.02 (30.54-40.85)	0.280
Elevated	11 (2.0%)	3 (1.5%)	8 (2.4%)	
Normal*	25.40-51.33	25.59-51.33	25.40-50.41	0.423
Decreased	26 (4.9%)	7 (3.5%)	19 (5.7%)	
$CD4^+/CD8^+$ cell ratio	1.42 (1.14-1.82)	1.42 (1.18-1.77)	1.42 (1.09-1.86)	0.746
Elevated	22 (4.1%)	8 (4.0%)	14 (4.2%)	0.427

Normal*	0.46-2.72	0.61-2.72	0.46-2.72	
Decreased	1 (0.2%)	1 (0.5%)	0 (0.0%)	
$CD8^+$ T cells (%)	25.20 (20.76-29.98)	25.17 (21.13-29.72)	23.35 (20.63-30.39)	0.820
Elevated	24 (4.5%)	10 (5.1%)	14 (4.1%)	
Normal	14.24-38.48	14.24-38.48	14.41-38.32	0.793
Decreased	19 (3.6%)	6 (3.0%)	13 (3.9%)	
NK cells (%)	16.89 (12.01-22.75)	16.07 (11.98-23.09)	17.42 (12.01-22.58)	0.668
Elevated	44 (8.2%)	15 (7.6%)	29 (8.6%)	
Normal*	3.51-30.44	4.58-29.66	3.51-30.44	0.852
Decreased	2 (0.4%)	1 (0.5%)	1 (0.3%)	

Data are presented as median (IQR) or n (%). *Data are shown as the normal ranges of the indicators. HCWs: health care workers. The comparison of continuous covariate between two groups was performed with Mann–Whitney U test. The comparison of categorical covariate between two groups was evaluated using χ^2 and Fisher's exact test.